Myeloproliferative Neoplasia Remodels the Endosteal Bone Marrow Niche into a Self-Reinforcing Leukemic Niche.

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Public Summary:
This study describes one of the key mechanisms by which clonal dominance of an unfit population of transformed HSCs is established. HSC function is largely influenced by the activity of BM niche cells, including mesenchymal stem cells (MSC) and their osteoblastic lineage cell (OBC) derivatives. Here, we use our inducible Scl-tTA::TRE-BCR/ABL double transgenic mouse model of human CML, to investigate how leukemic hematopoiesis impacts on the supportive function of the BM niche. First, we demonstrate that the phenotypically identifiable endosteal OBCs contains most of the cells known from mouse genetic studies to have HSC-supporting activity. Second, we show that CML development causes a severe remodeling of the BM microenvironment and negatively affects the HSC-supporting activity of OBCs. Strikingly, we find that this remodeling is a consequence of malignant myeloid cells directly stimulating MSCs to overproduce functionally altered OBC derivatives, which accumulate in the BM cavity as inflammatory myelofibrotic cells. These remodeled OBCs, in turn show profound molecular and functional deregulations, and favor myeloid differentiation at the expense of HSC maintenance. Our results describe a novel and important self-reinforcing mechanism that affects the complex crosstalk between hematopoietic and stromal cells in the BM microenvironment, and contributes to the development of myeloid malignancies. Moreover, they identify a new route for the pathogenesis of BM myelofibrosis occurring in CML, and provide a mechanism for the loss of normal hematopoiesis that accompanies the development of these blood diseases. Altogether, they significantly advance our understanding of the cellular lineages that comprise the endosteal BM niche and uncover a critical relationship between leukemic hematopoiesis and the BM microenvironment, which could be used to develop new therapeutic strategies aimed at targeting the leukemic BM niche. This article was previewed in Cell Stem Cell (13:257-258, 2013), selected for Faculty of 1000 Biology, and highlighted as issue cover.

Scientific Abstract:
Multipotent stromal cells (MSCs) and their osteoblastic lineage cell (OBC) derivatives are part of the bone marrow (BM) niche and contribute to hematopoietic stem cell (HSC) maintenance. Here, we show that myeloproliferative neoplasia (MPN) progressively remodels the endosteal BM niche into a self-reinforcing leukemic niche that impairs normal hematopoiesis, favors leukemic stem cell (LSC) function, and contributes to BM fibrosis. We show that leukemic myeloid cells stimulate MSCs to overproduce functionally altered OBCs, which accumulate in the BM cavity as inflammatory myelofibrotic cells. We identify roles for thrombopoietin, CCL3, and direct cell-cell interactions in driving OBC expansion, and for changes in TGF-beta, Notch, and inflammatory signaling in OBC remodeling. MPN-expanded OBCs, in turn, exhibit decreased expression of many HSC retention factors and severely compromised ability to maintain normal HSCs, but effectively support LSCs. Targeting this pathological interplay could represent a novel avenue for treatment of MPN-affected patients and prevention of myelofibrosis.